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THE TOXIC CHARACTER OF THE COLOSTRUM IN PARTURIENT PARESIS.*

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In our first article on the resemblances between parturient paresis and eclampsia we have given the essential characteristics of both of these diseases. There is, therefore, no need to go into this subject farther, except to say that parturient paresis is a disease which among the lower animals seems to be confined to plethoric cows and heavy milkers. As pointed out by Law,[1] it is essentially a disease of the cow by reason of the fact that, of all domestic animals, the cow alone has been bred long and systematically for the purpose of securing the greatest powers of digestion and assimilation and the highest yield of milk. In other words, as the result of careful breeding the cow has been converted into a living machine for the transformation of various food-stuffs into milk. Parturient paresis is pre-eminently a disease of plethoric, heavy-milking breeds of cows and of those individual animals which give the greatest yield of milk. The disease is rare or unknown in the scrub cow or among common herds, and it is fatal in the best milking breeds. It is influenced by age, feeding, ease of calving, drying up of the milk secretion before calving, parturition, such weather conditions as influence the character and abundance of the food supply, and by certain individual idiosyncrasies and constitutional predispositions, by cardiac hypertrophy and by increased blood tension in the arteries and capillaries and by the driving of the blood from the great vascular viscera back of the diaphragm, as the result of severe compression, in the expulsive movements of labor. Emotional excitement must be practically excluded as a cause of this disease. Among the prime and immediate causes we have parturition, a permanent or transient plethoric condition of

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* Received for publication February 13, 1912.

[1] *Text-book of Veterinary Medicine*, 2d ed., 3, pp. 301–17. Ithaca, N.Y., 1905. This book contains the best account of parturient paresis that we have thus far seen.

the blood vessels, with corresponding increase of pressure on the nerve centers of the brain, the phenomenal trophic and secreting activity of the udder of heavy milkers and the intensely active physiological activity of the mammary glands, resulting in the sudden rise and absorption into the circulation of leukomaines or toxic alkaloids of the cells of the mammae. These, according to Law, are the principal causes operating to bring on an attack of this disease. In the present state of our knowledge it is of little moment whether we call the substances other than milk resulting from the sudden disintegrative changes occurring in the udder at, or about the time of parturition, leukomaines, alkaloids, toxins, or what not. It seems reasonably certain, however, that no gland of the size and physiological activity of the udder of a heavy milking cow but must contribute largely and sometimes malignantly to the internal secretions of the animal. The question, therefore, immediately before us in the study of this acutely toxic condition in the cow, is to determine experimentally whether immediately preceding or during an attack of this disease the udder does actually secrete poisonous substances which if not quickly eliminated or prevented from entering the blood-current could be held responsible for this disease. It therefore occurred to one of us, Kastle, to test the conduct of the first colostrum of the cow, obtained during an attack of parturient paresis, upon the lower animals.[1] Accordingly these tests have been carried out on the guinea-pig.

Our experiments have also included a few other substances besides the colostrum of cows suffering from parturient paresis, such as the first colostrum of the normal cow, fresh milk from the Station herd, the urine of the normal cow and the first urine of a cow suffering from parturient paresis, normal salt solution, (0.85 per cent NaCl), and the aqueous solution of certain residues from colostrum and milk left after precipitating the colostrum and milk with dilute acid, and evaporating. In the following we give the results of these experiments under their respective headings as to the substances tested.

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[1] On the day after our three papers on parturient paresis and eclampsia were mailed to the editor of the *Journal of Infectious Diseases*, Chicago, viz, on February 13, 1912, Dr. Surface called our attention to an abstract by Helfer of a paper by Hoyois in the *Berliner Tierärztliche Wochenschrift*, October 5, 1911, No. 40, pp. 727–28, the original of which appeared in the *Annales de Médicine vétérinaire de Bruxelles*, July–Aug.–Sept., 1910?, in which according to Hoyois the colostrum in cases of parturient paresis, on intraperitoneal injection in doses of 10 to 20 gms., caused paralyzing symptoms in rabbits and guinea-pigs, with subsequent death at the end of seven to 12 days.

FRESH MILK.

Experiment 1.—A healthy male guinea-pig received into the peritoneal cavity by hypodermic injection, 5 c.c. of fresh milk containing 22,500 bacteria per c.c. This pig seemed distressed for an hour or so, and then ate a little. On the following morning he had some diarrhea, from which he promptly recovered. One month later he was alive and well.

Experiment 2.—A healthy male guinea-pig received into the peritoneal cavity, by hypodermic injection, the dried residue of the filtrate of 200 c.c. of fresh milk, which had been precipitated with alcohol. The dried residue was rubbed up with 10 c.c. of sterile distilled water before injecting. This pig showed no discomfort, had no diarrhea. One month later he was alive and well.

COLOSTRUM FROM NORMAL COW.

Experiment 3.—A healthy male guinea-pig received into the peritoneal cavity, by hypodermic injection, 5 c.c. of fresh, first colostrum from a normal cow. This colostrum contained 3,000 bacteria per c.c. mostly streptococci. This pig seemed distinctly distressed for remainder of day. The following morning he had a bad diarrhea from which he promptly recovered. One month later he was alive and well.

Experiment 4.—A healthy male guinea-pig received into the peritoneal cavity by hypodermic injection, 5 c.c. of fresh colostrum from a normal cow which had calved 60 hours previously. The cow had induration of one quarter of the udder. No bacterial count was made of this colostrum. This pig seemed distressed for an hour or so, and then ate some. The following morning he had some diarrhea from which he promptly recovered. One month later he was alive and well.

Experiment 5.—A healthy, male guinea-pig received into the peritoneal cavity, by hypodermic injection, the dried residue of the filtrate of 100 c.c. of fresh first colostrum prepared as in Experiment 2. This pig showed no discomfort and had no diarrhea. One month later he was alive and well.

Experiment 6.—A healthy, male guinea-pig received into the peritoneal cavity, by hypodermic injection, the dried residue from 100 c.c. of fresh colostrum from a cow which had calved 60 hours before colostrum was obtained. The material was prepared as in Experiment 2. This pig showed no discomfort, the following morning he had a diarrhea from which he promptly recovered. One month later he was alive and well.

Experiment 7.—A healthy guinea-pig (sex not observed) received into the abdominal cavity, by hypodermic injection, 3 c.c. of the fresh, first colostrum from a normal cow, which had been diluted one in three with water. This pig showed no discomfort, two days later had a slight diarrhea. It now received in a similar manner 5 c.c. of the colostrum diluted with equal volume of water. The following morning had diarrhea which continued several days. One month later the pig was alive and well.

Experiment 8.—A healthy guinea-pig (sex not observed) received into the abdominal cavity, by hypodermic injection, 2.5 c.c. of colostrum whey which had been obtained by precipitating the colostrum with acetic acid, filtering and neutralizing the filtrate with N/10 sodium hydroxid and diluting with four times its volume of water. This pig showed no discomfort, had no diarrhea. Two days later received 5 c.c. of colostrum whey diluted with equal volume of water and prepared as above. The pig showed no discomfort, had no diarrhea. One month later he was alive and well.

COLOSTRUM FROM COW ILL WITH PARTURIENT PARESIS.

Experiment 9.[1]—A healthy, female guinea-pig received, in the manner above indicated, 10 c.c. of fresh, first colostrum from a cow ill with parturient paresis. The colostrum contained 34,600 bacteria per c.c. This pig seemed well for six days, had no diarrhea at any time, and then died. On post-mortem examination this pig showed acute parenchymatous nephritis with interstitial hemorrhages, acute parenchymatous hepatitis with interstitial hemorrhages, acute degeneration of the cells of the adrenal cortex, with complete destruction of the medullary cells, and interstitial hemorrhages. (Fig. 1, 2, 3.) There was no evidence of tuberculosis. The pig was not pregnant. Cultures from the liver, kidney, and spleen were negative. No peritonitis.

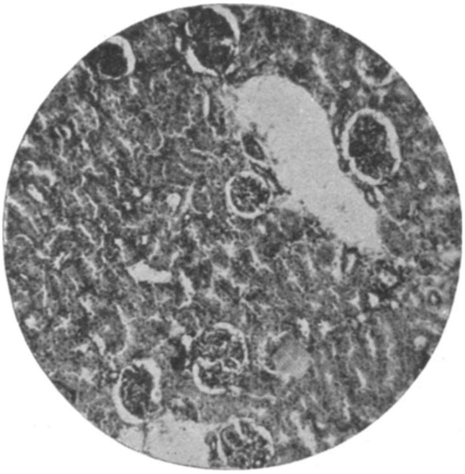

FIG. 1.—Experiment 9. Acute Nephritis. ×100.

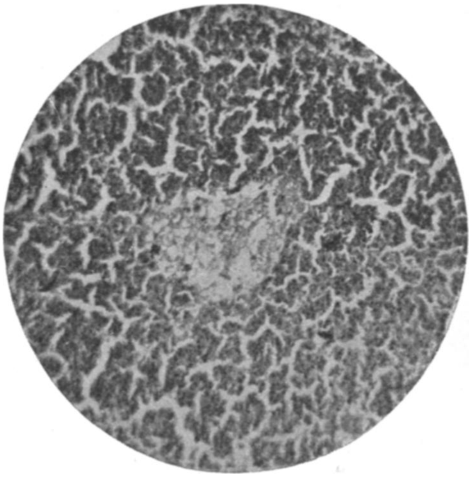

FIG. 2.—Experiment 9. Liver: Focal Necrosis. ×100.

Experiment 10.—A healthy, female guinea-pig received as above indicated 10 c.c. of the fresh, first skimmed colostrum from a cow ill with parturient paresis. This pig seemed well and had no diarrhea for five days and then died. On post-mortem this pig showed acute parenchymatous nephritis, with interstitial hemorrhage; acute parenchymatous hepatitis with interstitial hemorrhage, and marked peripheral necrosis; acute degeneration of cells of the adrenal cortex, with complete destruction of the medullary cells, and interstitial hemorrhages. (Fig. 4, 5, 6, 7.) There was no evidence of tuberculosis. The pig was in the very early stages of pregnancy. Cultures from the liver, kidney and spleen were negative. No peritonitis.

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[1] In our abstract of this paper published in the *Proceedings for the Society of Experimental Biology and Medicine*, pigs 9, 10, and 11 are referred to by the numbers 1, 2, and 3, respectively.

Experiment 11.—A healthy, female guinea-pig received in the manner above indicated 10 c.c. of fresh, first colostrum cream of a cow ill with parturient paresis. This pig seemed well and had no diarrhea for six days, and then died. Aborted during the first 12 hours. Fetus 5.5 cm. long. On post-mortem this pig showed acute parenchymatous nephritis, with interstitial hemorrhages, acute parenchymatous hepatitis, with areas of complete necrosis, and interstitial hemorrhages. Some degeneration of the cells of the adrenal cortex, with complete destruction of medullary

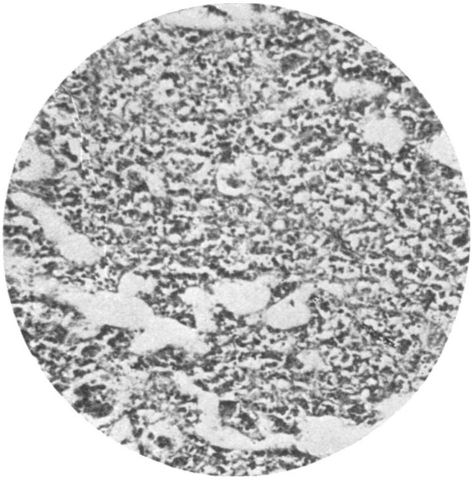
FIG. 3.—Experiment 9. Adrenal: Necrosis of Medulla. ×100.

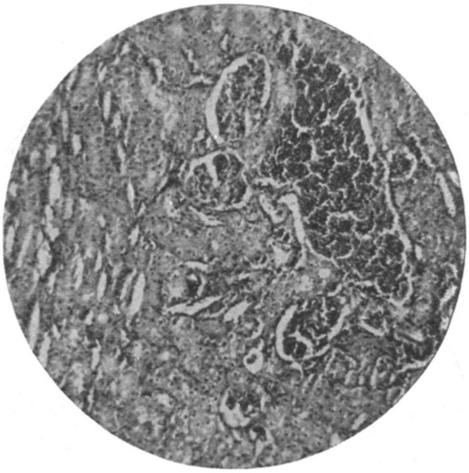
FIG. 4.—Experiment 10. Acute Nephritis: Hemorrhage. ×100.

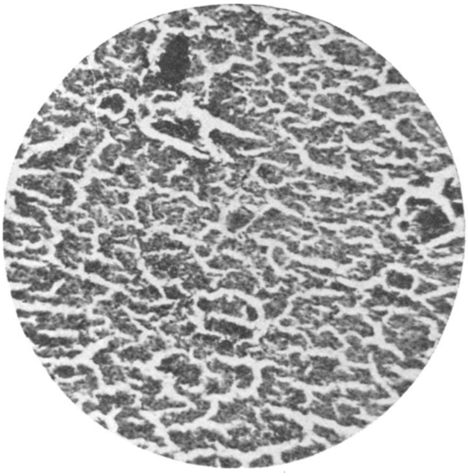
FIG. 5.—Experiment 10. Liver: Hepatitis; Hemorrhage. ×100.

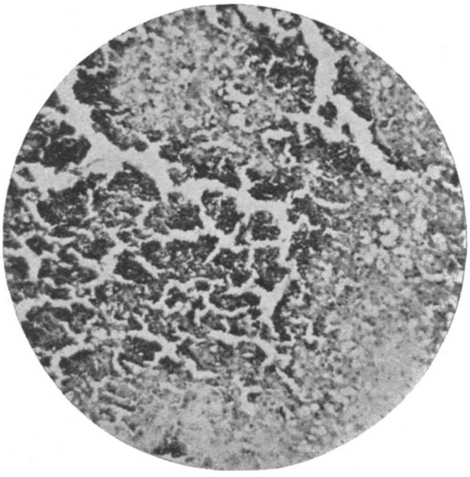
FIG. 6.—Experiment 10. Adrenal Cortex: Hemorrhage. ×100.

portion and interstitial hemorrhages. (Fig. 8, 9, 10, 11.) Acute lobar pneumonia of left lung. There was no evidence of tuberculosis. Cultures from liver, kidney and spleen negative. Culture from lung contained a diplococcus; no peritonitis except over upper and anterior surfaces of liver.

Experiment 12.—A healthy, female guinea-pig received, as above indicated, 10 c.c. of skimmed colostrum of a cow ill with parturient paresis, which had been kept 17 days at 8° C. The colostrum was very acid, reaction equal to 10.5 per cent normal sodium hydroxid. This pig steadily lost weight, otherwise seemed well, had no diarrhea and lived 16 days, then died.

Experiment 13.—A healthy, female guinea-pig received, as above indicated, 10 c.c. of the 17-day old colostrum, which had been neutralized with normal sodium hydroxid. The colostrum was from a cow ill with parturient paresis. This pig steadily lost weight, has not seemed quite well at any time. Had no diarrhea. Aborted on the fifth day. Fetus was 8 cm. long. This pig is still living, and is regaining weight. There is a slight increase in the quantity of urine which contains albumen.

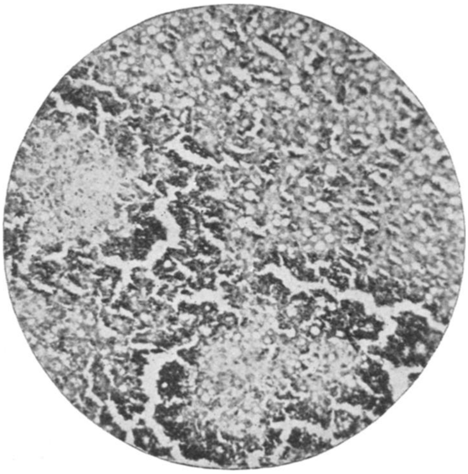

FIG. 7.—Experiment 10. Adrenal Cortex: Necrosis; Hemorrhage. ×100.

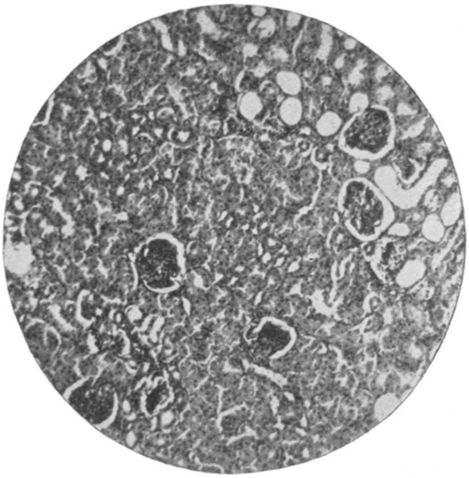

FIG. 8.—Experiment 11. Acute Nephritis. ×100.

Experiment 14.—A healthy, female pig received, as above indicated, 10 c.c. of 17-day old colostrum which had been neutralized with normal sodium hydroxid and boiled. Colostrum was from a cow ill with parturient paresis. This pig steadily lost weight, had no diarrhea, aborted within the first 12 hours. Fetus 8 cm. long. This pig is still alive, and is regaining weight. There is a slight increase in the quantity of urine which contains albumen.

NORMAL SALT SOLUTION ON PREGNANT GUINEA-PIGS.

Experiment 15.—A healthy, female guinea-pig, five to seven weeks pregnant, received into the abdominal cavity, by hypodermic injection, 10 c.c. of sterile, normal salt solution (0.85 per cent NaCl) at 38° C. This pig showed no discomfort and had not aborted at the end of five days. Had no diarrhea. At the end of five days from the time the pig had received the injection of normal salt solution she received intraperitoneally by injection 10 c.c. of the fresh milk from the Station herd, which had previously been heated to 38° C. This caused no discomfort and no diarrhea. She had not aborted at the end of four days. At the end of this time she received by intraperitoneal injection 8 c.c. of the first, fresh, whole colostrum of a normal cow (second calf), which had previously been heated to 38° C. Following this injection,

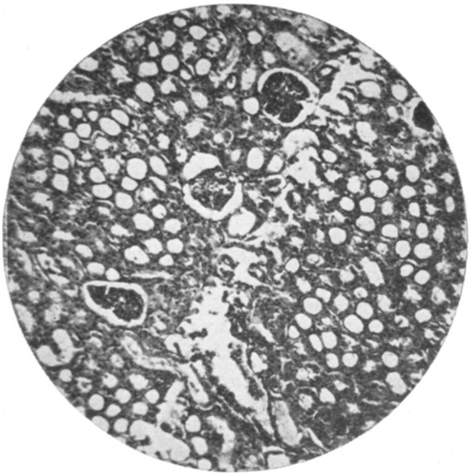
FIG. 9.—Experiment 11. Nephritis: Destruction of epithelial cells. ×100.

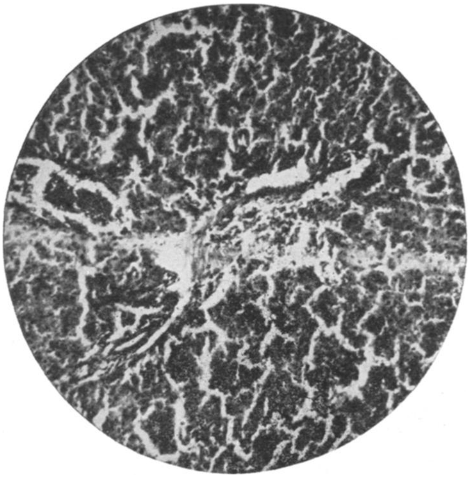
FIG. 10.—Experiment 11. Liver: Hepatitis; Hemorrhage. ×100.

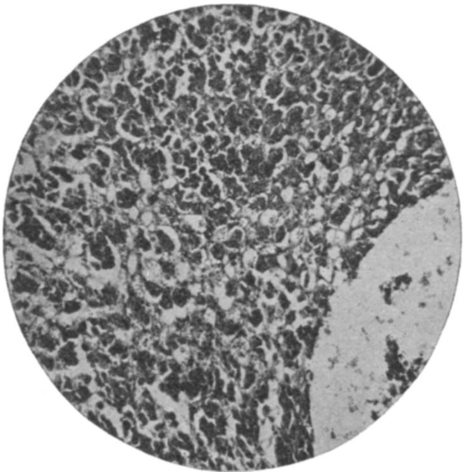
FIG. 11.—Experiment 11. Adrenal: Necrosis of Cortex and absence of Medulla. ×100.

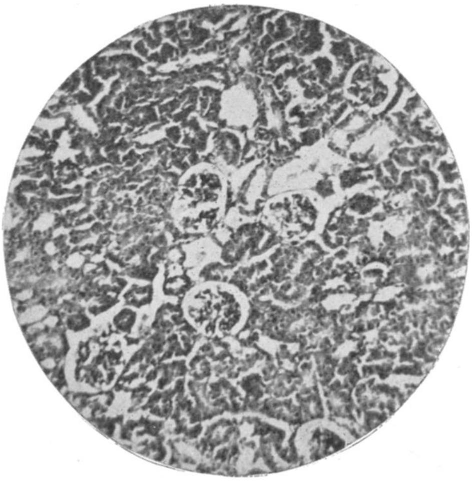
FIG. 12.—Experiment 18. Acute Nephritis. ×100.

this pig aborted in 60 hours, giving premature birth to two fetuses, each 6.5 cm. in length, and 60 hours after this she aborted a second time, giving premature birth to one fetus, 7 cm. in length.

FRESH MILK FROM STATION HERD ON PREGNANT GUINEA-PIG.

Experiment 16.—A healthy, pregnant guinea-pig received, by intraperitoneal injection, 10 c.c. of fresh milk from Station herd, the milk being previously heated to 38° C. before the injection. This pig suffered some discomfort from the injection but had not aborted at the end of five days. She was not well, however, showing loss of appetite and falling off in weight. At the end of five days the pig was chloroformed. The post-mortem showed accumulation of blood in left side of peritoneal cavity, and some unabsorbed particles of cream over omentum. Pregnant in left horn of uterus, two fetuses, 1 cm. in length. Right horn of uterus empty, and evidently had not been pregnant. The bad condition of this pig was undoubtedly due to puncture of a blood-vessel in the peritoneal cavity, as a result of the injection.

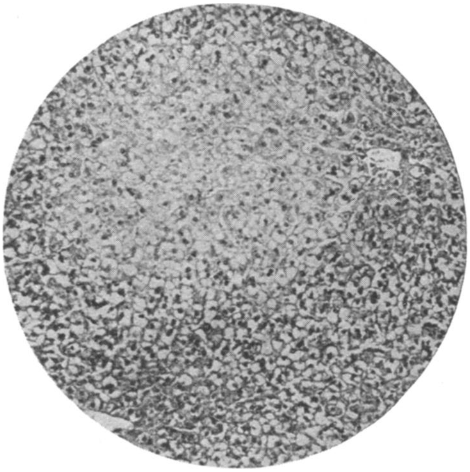
FIG. 13.—Experiment 18. Liver: Necrosis. ×100.

COW'S URINE.

Experiment 17.—A healthy, male guinea-pig received, as above indicated, 10 c.c. of fresh clear urine of normal cow. This pig showed no discomfort, had no diarrhea, and no diuresis. Lived seven days and was then chloroformed. On post-mortem, organs and tissues were found normal.

Experiment 18.—A healthy, male guinea-pig received, as above indicated, 10 c.c of the first, fresh, clear urine of a cow ill with parturient paresis. This pig showed no discomfort, and no diarrhea, but had a very marked diuresis, passing at least 200 c.c. urine in 24 hours. This urine contained a small amount of albumen and no sugar. This pig recovered from the diuresis and seemed well and was chloroformed on the thirteenth day. The post-mortem showed small areas of acute parenchymatous nephritis, without interstitial hemorrhages, rather extensive necrosis of the liver cells, especially in the periphery of the lobules, but without interstitial hemorrhages. Localized areas of necrosis in the adrenal cortex, with normal medullary layer. (Fig. 12, 13.)

It is evident from these results that normal salt solution, fresh milk from normal cows, the colostrum of normal cows, and the urine of a healthy cow cause no serious disturbances in the normal guinea-pig, when injected into the peritoneal cavity. The injection of the colostrum of normal cows invariably caused a diarrhea in healthy guinea-pigs, male and female, from which they gradually recovered after a few days. In this connection it is interesting to note that it has long been known that human colostrum acts as a mild cathartic on the suckling.[1] As already indicated in the above (see Experiment 16), the pregnant guinea-pig that received the injection of the milk of a healthy dairy herd did experience a good deal of discomfort immediately following the injection. This was followed by loss of appetite and corresponding loss of weight, during the four days that the pig lived. On January 29 this pig was chloroformed. The post-mortem showed a rupture of one of the blood vessels in the peritoneal cavity, and in all probability the abnormal condition of this pig after the injection of the fresh milk was the result of slow bleeding into the body cavity. No evidence was obtained to show that the pig had aborted. With this possible exception which evidently resulted from accidental, mechanical injury, and with the exception of the diarrhea resulting from the injection of normal colostrum, no noteworthy disturbances followed from the intraperitoneal injection of normal salt solution, fresh milk, normal colostrum, or the urine of the normal cow. On the other hand, death resulted from the injection of the colostrum of the cow having parturient paresis, and the post-mortem and microscopical examinations of the organs of the four guinea-pigs that were thus killed showed the same pathological degenerations and changes that are characteristic of eclampsia. Unfortunately but little if anything seems to be known regarding the micropathology of parturient paresis in the cow. We have shown, however, that cows recovering from an attack of this disease invariably show a nephritis. Our results with the colostrum of the cow suffering with parturient paresis certainly go to show the presence therein of some substance toxic to guinea-pigs and certainly point to the udder and the mammary glands as the place of origin of the toxins or internal secretions producing parturient paresis and eclampsia respectively. The fact that the urine of the cow ill with parturient paresis causes such a profound diuresis in the guinea-pig also points to the presence of toxic substances in the urine of the animals so affected and indicates that these toxins are not entirely destroyed in the tissues of the cow, but are in part at least, and it may be in somewhat modified form, excreted by the kidneys.

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[1] Williams, *Obstetrics*, New York, 1908, pp. 351–52.

The fact also that the colostrum of the cow during an attack of parturient paresis invariably caused an abortion in pregnant guinea-pigs is a matter of considerable physiological significance and will be discussed more fully in the following paper.

We hope in the near future to attempt the isolation of the particular substance in the colostrum or the udder responsible for parturient paresis, or, at any rate, its more careful study and accurate identification, and also to undertake a careful microscopic and chemical study of the mammary gland in this condition. Obviously this must be deferred until we can obtain the material necessary for this investigation.

The idea that parturient paresis is the result of some toxic internal secretion product elaborated in the udder of the cow, its absorption into the blood and action on the nerve centers, is in harmony with all that is known concerning the etiology of this disease and with the modern therapeutic practices which have proven of such inestimable benefit in its treatment and cure. In this connection it is only necessary to point that these several modes of treatment have affected a reduction in the mortality of this disease from 70 to 15 and finally to less than 1 per cent, and can be most readily explained on the assumption that through extreme dilatation of the udder by oxygen or sterile air, the blood supply of the mammary gland is practically cut off entirely or at any rate greatly diminished, until the milk gland has the opportunity to resume its ordinary excretory activity, thereby eliminating the toxic products in the colostrum and the milk.

In 1897 Schmidt effected a great reduction in the mortality from this disease by the use of sterile solutions of potassium iodid. Later aqueous solutions of other antiseptic substances were found equally efficacious and still later it was found that normal salt solutions accomplished the same result. Obviously no antiseptic or antidotal properties can be described to an 0.85 per cent solution of common salt. In this connection the practice of the Jersey Island dairymen is of great interest. This consists merely in leaving the udder unmilked for 24 hours after calving. In this way their predisposed cows were protected against an attack of parturient paresis. Obviously in such cases the necessary dilatation of the udder was effected through its own secretions. Finally there came into modern veterinary practice the use of oxygen gas and later the use of sterilized air, whereby the mortality from this disease was reduced to less than 1 per cent. Here the dilatation necessary to the prevention of the absorption of poisonous products is produced by a comparatively inactive mixture of gases, its only other possible effect being to maintain an aerobic condition of the udder, until the gland has had the opportunity to resume its normal excretory functions. Upon no other grounds than those involving the elaboration within the udder, at the period of parturition, of toxic substances and the passage of these into the blood stream, do we have so complete an understanding of the saving of animal life by the therapeutic methods now employed in the treatment of parturient paresis. While by no means an uncommon pathological condition among plethoric, heavy-milking dairy cows, it is not always an easy matter to secure a case of this disease at the moment when it is desired. We therefore reserve the right to continue these investigations along the lines indicated in the above, with the object of throwing further light on the nature of the toxin contained in the colostrum of cows suffering with parturient paresis, and the possible occurrence of this toxin in the colostrum of women suffering from eclampsia, and with the still further object of studying the precise conditions under which it is elaborated in the udder and mammary glands.